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## Clinical Trials

### Part 3

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## DEFINING THE STUDY POPULATION, INTERVENTIONS AND ENDPOINTS

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## Study Population

- Should be defined in advance
- Unambiguous inclusion (eligibility) criteria
- Must consider impact on
  - Study design
  - Ability to generalize
  - Participant recruitment

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## Types of inclusion criteria

- Inclusion
  - Define the medical condition of interest
- Exclusion
  - Cases unlikely to respond
  - Conditions for which it is unethical to randomize
  - Safety
  - Measurement problem
  - Subject unreliable/unwilling
  - Administrative/regulatory/other

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## Example – VA CSP #468

- Surgical and Medical Treatments for Parkinson's Disease
  - Comparison of Best Medical Therapy to Deep Brain Stimulation
  - Comparison of STN to GPi stimulation
- Inclusion Criteria
  - Idiopathic Parkinson's disease
  - Hoehn and Yahr stage 2 or worse when off medications
  - L-dopa responsive with clearly defined "on" periods
  - Persistent disabling symptoms
  - Stable on medical therapy for at least one month

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## Example – VA CSP #468 Exclusions

- Cases unlikely to respond
  - "Parkinson's plus" syndromes
- Unethical to randomize/safety
  - Previous Parkinson's Disease surgery
  - Medical contraindications to surgery or stimulation
  - Contraindication to MRI
  - Score on Mini-Mental Status examination of 24 or lower, or other neuropsychological dysfunction that would contraindicate surgery
  - Intracranial abnormalities
  - Pregnancy

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## Example – VA CSP #468 Exclusions

- Unreliable/unwilling
  - Not available/willing to be followed according to study protocol
  - Unwilling to consent
  - Active alcohol or drug abuse
- Administrative/regulatory/other
  - Age less than 21
  - Concurrent participation in another research protocol

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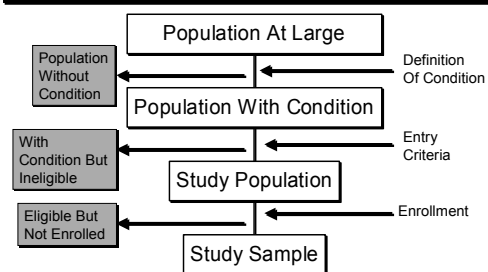
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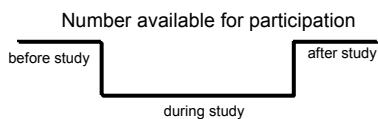
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## Overestimating Ability to Recruit

- 5-10% of screened patients are enrolled
- 80% of studies fail to meet recruitment targets on time
- Lasagna's Law




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## Estimating Recruitment

- Recruitment from previous similar studies
- Past recruitment for this site/investigator
- Estimates of patient availability from centralized databases
- Pilot study
- Past performance is usually indicative of future results

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## Recruitment Strategies

- Inpatients, outpatient clinics
- Chart reviews
- Clinic, pharmacy lists
- Referrals from other caregivers
- From presentations
- Direct mailings, fliers
- Arrangements with Vets' orgs.
- Internet website
- Media campaigns

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## Adaptive Recruitment Solutions

- Extend recruitment period
- Replace/add sites
- Broaden inclusion
- Revise sample size estimate
  - Reduce power
  - Increase treatment effect difference of interest
  - Update estimates of variability
  - Use a more sensitive statistical technique
- Reduce workload/streamline protocol

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**Example: VA CSP #399**

- Effect of antiarrhythmic therapy on maintenance of sinus rhythm in patients with atrial fibrillation
- Treatment arms
  - Amiodarone, Sotalol, Placebo
- Inclusion criteria
  - 72hrs of continuous AF (upper limit 12 months)

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**Example: VA CSP #399**

- Sample size: 1260
- Power 85%
- Primary outcome measure: recurrence rate at 1 year of follow-up
- Expected treatment effects
  - 35% on placebo
  - Either drug at least 15% better than placebo
  - One drug at least 10% better than the other
- 28 sites
- 30 months intake

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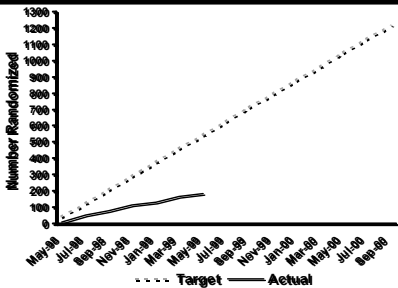
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**Randomization Timeline as of May, 1999**



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## Study Modifications

- Allowed inclusion of patients with AF duration > 12 mos.
- Dropped 8 underperforming sites
- Reallocated funding to high recruiters
- Extended intake by 12 months
- Redefined primary outcome measure
  - Time to recurrence of atrial fibrillation
  - All other sample size assumptions unchanged
  - Reduced sample size from 1260 to 706

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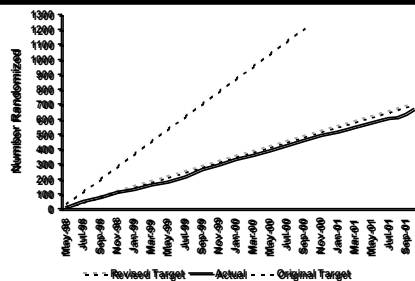
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## Final Randomization Timeline



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## DEFINITIONS

- Intervention - A treatment or procedure assigned to a subject or population to reduce the burden of illness caused by a disease or condition
- Endpoint - The event(s) or measurement(s) observed during or after an intervention that are used to evaluate the success or failure of the intervention

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## DEFINITIONS

- Experimental treatment
  - Effect not established
  - Existing studies not convincing
- Standard treatment
  - Standard of care
  - Effectiveness may or may not have been rigorously established
- Control group
  - Comparison group against which the experimental treatment will be compared

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## TYPES OF INTERVENTIONS

- Drugs, Vaccines, Gene Therapy
- Surgical or Medical Procedures
- Medical Devices
- Diagnostic and Screening
- Lifestyle or Diet
- Psychiatric Therapy
- Healthcare Delivery Systems
- Complementary and Alternative Therapies

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## Factors Affecting The Choice Of The Intervention

- Maximize benefit, minimize toxicity
- Can be standardized
- Will not be affected by altered clinical state
- Acceptance/Compliance
- Blinding
- Availability of drug or procedure

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## Factors Defining an Intervention

- Medications
  - Dose
  - Frequency
  - Duration
- Surgical
  - Standardized and Specific Procedures/Techniques
  - Types of equipment/instruments
  - Skill level of interventionist

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## TYPES OF COMPARISONS

- Experimental vs. control
  - Control may be active treatment or placebo
- Standard vs. control
  - Treatment in widespread use without rigorous evidence
  - Treatment extended to a group without established benefit
- Special cases
  - No control
  - Experimental versus experimental

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## CLASSICAL DESIGN

- Placebo Control Trial
  - Treatment A – Placebo Control
  - Treatment B – Active Drug
- Active Control Trial
  - Treatment A – Drug X (Standard)
  - Treatment B – Drug Y (Experimental)
- Placebo not ethical if there is effective standard therapy

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**“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”**

Declaration of Helsinki

[http://www.wma.net/e/policy/17-c\\_e.html](http://www.wma.net/e/policy/17-c_e.html)

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## **SCIENTIFIC RATIONALE FOR PLACEBOS**

- Establishing a reference point
- Focuses on efficacy
- Smaller studies
  - strength of an association
  - statistical variability

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## **STUDY DESIGNS**

- Choice of interventions provides the underlying statistical design structure for a trial
  - Two or multiple groups?
  - Factorial designs – two or more interventions tested in the same experiment in such a way that all possible combinations of treatments are possible
  - Crossover designs – more than one intervention sequentially assigned to each subject

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## FACTORIAL DESIGN

	Drug X	Placebo X
Drug Y	Drug X + Drug Y	Placebo X + Drug Y
Placebo Y	Drug X + Placebo Y	Placebo X + Placebo Y

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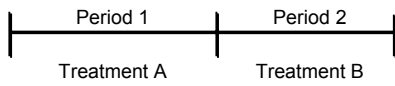
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## CROSSOVER DESIGN



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## More Complex Interventions

- Multiple Drugs vs. Placebo Control
- Combinations of treatments
  - Drug combination 1 vs. combination 2
- Different lengths of treatment
- Different starting times
  - At enrollment or at onset of symptoms
  - Drug holiday vs. no drug holiday
- Withdrawal studies

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## Special Problems in Studies of Procedures

- Standardizing the intervention
- Variability in experience / technique
- Appropriate control group
- Blinding
- Time delay from randomization to treatment

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## VA CSP #246: TURP vs WW for BPH

- Main question: Is surgery necessary?
- Conducted at 9 VAMC's (1986-92)
- TURP
  - Standard of care, widespread use, little need to standardize the procedure, effectiveness study
  - Window of 2 weeks from randomization to surgery allowed
- Watchful Waiting
  - Brochure describing behavioral strategies which may help them cope with their symptoms

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## VA CSP #246: TURP vs WW for BPH

- Follow-up
  - Six weeks and semiannually for 3-6 years
  - Telephone calls every 2 months
  - internal medicine rather than urology
- Primary outcome measure
  - Percentage of patients not having a clinically important rise in BPH symptom score nor a serious GU event (e.g. retention, creatinine rise, incontinence)
- Other outcomes
  - Quality of life
  - Cost-effectiveness

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## VA CSP #246: TURP vs WW for BPH Results

- TURP was more effective
  - Primary outcome measure and QOL
- However, most men will do well with WW
- Cross-overs/compliance
  - 10% of those randomized to TURP never had surgery
    - Those with less bother from BPH symptoms
  - 27% of those randomized to WW eventually had surgery
    - Those with more bother
- Results were consistent regardless of how cross-overs were treated in analysis

Emergency Operation (E). Any patient in one of the classes listed previously who is operated on as an emergency is considered to be in poorer physical condition. The letter E is placed beside the numerical classification. Thus, the patient with a bilateral uncomplicated hernia now incarcerated and associated with nausea and vomiting is classified as IV-E.

### 2. Description of TURP Surgery:

The only standardized requirement of this protocol for TURP is that it be performed by a staff urologist or a urology resident during the final clinical year of urological training. Otherwise, the urologist's discretion will determine the following items which will be recorded on the Surgery Form (Form 8).

- The duration of the procedure in minutes.
- Which type of anesthesia was utilized.
- How much IV fluid was used within 24 hours.
- How many transfusions were used within three days.
- Which anatomical lobes of the prostate were removed and the amount of tissue removed in grams.
- Which technique of resection was used, enucleation or cross-stepping. Only complete resections will be considered.
- Which incidental procedures such as prostatectomy, vasectomy, urethral dilatation and urethrotomy were performed.
- Which prophylactic antibiotics was administered and the number of days it was given.
- Whether the resection was complete. If judged complete, was it resected to the surgical capsule. If incomplete, what was the reason for not completing the procedure.
- Whether reanastomosis was required, and if so, the reason and number of days.

Transurethral prostate surgery is usually limited to about an hour because of the possibility of excessive fluid absorption (65). Nonchemolytic fluids, such as glycine 1.5%, urine 1.0% or sorbitol 5% are usually used as irrigants although some workers still use sterile water in conjunction with IV mannitol (61, 62) for better visualization.

The amount of tissue removed varies with the experience of the operator, but in general, should not exceed that which can be removed within the time limitation. Some surgeons will not routinely resect more than 50 gms. Large glands may best be removed by enucleation methods (63, 64) and smaller ones by cross-stepping with the electrocautery device, but the surgeon must make the final decision.

Instrumentation is now refined, with most operators using fiberoptic light sources and either insulated or continuous flow resectoscopes, 24-26F in either, each of which has its advantages (63). A few centers use the Thompson direct vision punch resectoscope. The inflow pressure should be between 70-100mm H<sub>2</sub>O by hanging the fluid containers two-and-a-half to three feet above the resectoscope tube (64). The hydrostatic pressure with the continuous flow device is designed to remain less than 100mm H<sub>2</sub>O within the urethra (65).

### 3. Postoperative Complications:

Although administration of prophylactic antibiotics is a controversial issue (66, 67), in this protocol antibiotics are utilized at least one hour prior to surgery and lasting up to five days postoperatively. (SMX-TMP 800mg IV two to four hours preoperatively repeated twelve hours postoperatively seems adequate) (66). In addition, more extensive prophylaxis for SBE in patients with abnormal cardiac valves or use in other patients with prostheses will be utilized as dictated by the particular clinical situation. Immediate but rare surgical complications include dilutional hyponatremia (Na less than 120) caused by fluid absorption (TUR syndrome), postobstructive diuresis, hyperglycemia and inappropriate ADH secretion, shock, perforation, urinary tract infection, epistaxis, thrombophlebitis, pulmonary embolus, DIC or fibrinolysis, abductor spasm and hemorrhage (63, 64) and ammonia toxicity from glycine.

Late post-TURP complications include delayed hemorrhage, incontinence, retrograde ejaculation and stricture formation (13).

Information regarding the surgical procedure and immediate surgical complications will be entered onto the Surgery Form (Form 8) by the urologist at the time of dictation of the operative note, and late complications will be

**VA CSP #456:**  
**Open vs Lap Hernia Repair**

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- Began 1/2001 at 12 VAMC's
- Treatments
  - Highly standardized
  - Surgeons must have demonstrated proficiency in the procedure
  - At each site, use "best" surgeon for each procedure
  - Efficacy rather than effectiveness

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**VA CSP #456:**  
**Open vs Lap Hernia Repair**

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- Follow-up
  - Up to 5 years
  - 1<sup>st</sup> year: post-op, 6 wk telephone, 3 mo visit, 6 month telephone
  - Annual visits

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**VA CSP #456:**  
**Open vs Lap Hernia Repair**

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- Primary Outcome Measure
  - Hernia recurrence at 2 years
  - Evaluation by independent surgeon
  - If recurrence detected, confirm by a second surgeon, ultrasound or operative report

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## VA CSP #456: Open vs Lap Hernia Repair

- Other outcomes
  - Complications
  - Pain
  - Time to return to normal activities
  - QOL
  - Patient satisfaction
  - Caregiver burden
  - Cost

### IX. OPERATIVE INTERVENTION

#### A. Standardization of Procedures

For all patients:

1. An IV dose of a 1<sup>st</sup> generation cephalosporin or equivalent will be given to the patient within 30 minutes prior to the incision with time, antibiotic, and dose recorded.
2. The patient's abdomen will be prepped in the usual manner.
3. Additional procedures performed will be recorded.

#### I. Laparoscopic herniorrhaphy

For the purposes of this study, either the transabdominal preperitoneal (TAPP) or the totally extra peritoneal (TEP) will be considered equivalent, as both are preperitoneal repairs. The selection of the type of laparoscopic repair will be left to the discretion of the surgeon.

#### TAPP

The technique described by Fitzgibbon et al will be used. All trocar sites of incision will be injected preemptively with 0.5% bupivacaine mixed 1:1 with 1% lidocaine. The first trocar site (umbilicus) will be injected blindly. The other trocar sites will be injected while watching through the laparoscope to ensure injection through all layers of the abdominal wall. Once intra-abdominal access has been established, a CO<sub>2</sub> pneumoperitoneum will be created, and the laparoscope introduced, allowing a thorough diagnostic laparoscopy. Additional trocars will be placed under direct vision and their size and location recorded. The peritoneum will be opened by making an incision on the ipsilateral side of the medial umbilical ligament, which can be divided if it appears to compromise exposure. This initial incision into the peritoneum will be made at least two centimeters above the myopectineal defect. The incision will be extended laterally towards the anterior superior iliac spine. The peritoneal flap will be mobilized inferiorly. The preperitoneal dissection will extend from the symphysis to just medial to the iliac vessels on Cooper's ligament. A lateral plane will be developed lateral to the epigastric vessels and superior to the cord structures. The vas deferens should be identified on the medial aspect of the cord structure. If a direct hernia is present, the sac and preperitoneal fat will be reduced from the hernia orifice. For indirect hernias, the sac will either be mobilized from the cord structures and reduced back into the abdomen or, for large hernias, divided at the internal ring, leaving the distal part *in situ*. An indirect inguinal hernia sac that is divided will be closed and the method of closure will be recorded. The dissection will be completed by completely mobilizing the peritoneal flap away from the cord structures proximal to the bifurcation of the internal spermatic vessels and the vas deferens. It is not necessary to dissect the inferior aspect of the cord. Once the dissection is complete, a piece of polypropylene mesh will be performed using a piece of polypropylene mesh. The size of the prosthesis will be at least 3 by 5 inches (7.62 cm x 12.7 cm). Any direct defect will be covered by a minimum of 2 cm of mesh. If needed, a second piece of mesh will be used and its size recorded. Whether or not the sac is tacked-up will be recorded. Staples or

tacks will be used for fixation and the number and location of staples or tacks will be recorded. The minimal number of tacks will be one tack in the subcutis with the mesh. There will be another tack placed just medial to the vein on Cooper's ligament. A third tack will be placed on the outer edge of the mesh just above the iliopectic track, superior medial to the anterior superior iliac spine.

The method of closure will be recorded. In order to avoid injury to the lateral femoral cutaneous nerve of the thigh or the femoral branch of the genitofemoral nerve, care will be taken not to staple below the iliopectic tract when lateral to the internal spermatic vessels. Staples will be oriented parallel to the nerves, i.e., vertically when stapling inferiorly. Superior and lateral placement of staples will be horizontal, corresponding to the direction of the ilioinguinal and iliohypogastric nerves. Additional analgesia (50 cc of dilute marcaine – 10 cc of 0.5% marcaine mixed with 20 cc of saline) may be instilled into the operative space and will be recorded.

The final step will be to close the peritoneum over the prosthesis. The peritoneum will be closed using either tacks or staples. Any remaining peritoneal defect will be recorded. Any trocar site 10 mm or greater will be closed. The method of closure, whether it be direct suture or direct suturing, will be recorded. Bilateral hernias will be repaired using two pieces of mesh that are overlapped in the middle. The skin will be closed with subcuticular sutures.

#### TEP

All trocar sites will be injected preemptively with 0.5% bupivacaine mixed 1:1 with 1% lidocaine. The first trocar site (umbilicus) will be injected blindly. The other trocar sites will be injected while watching through the laparoscope to ensure injection through all layers of the abdominal wall. The skin and fascia at the umbilicus will be incised as if one were performing an open laparoscopy but the peritoneum will be left intact. Access to the preperitoneal space will be accomplished using one of these methods:

- a.) digital dissection to create a large enough space to accommodate a Hasson cannula. An operative laparoscope will then be introduced and complete dissection will be accomplished using sharp and blunt dissection;
- b.) a water or air-filled balloon dissector will be employed to complete the dissection after the skin and fascia have been opened;
- c.) a visipoint will be used to access the preperitoneal space.

Regardless of the technique, the abdominal cavity will not be entered intentionally during the procedure. Additional trocars will be placed under direct vision and their size and location recorded. The preperitoneal dissection will extend from the symphysis to just medial to the iliac vessels on Cooper's ligament. A lateral plane will be developed lateral to the epigastric vessels and superior to the cord structures. The vas deferens should be identified medially. If a direct hernia is present, the sac and preperitoneal fat will be reduced from the hernia orifice. For indirect hernias, the sac will either be mobilized from the cord structures and reduced back into the abdomen, or if the sac is large, divided at the internal ring leaving the distal part *in situ*. The

proximal divided hernia sac will be closed and the method of closure will be recorded. The dissection will be completed by completely mobilizing the peritoneal flap away from the cord structures proximal to the bifurcation of the internal spermatic vessels and the vas deferens. It is not necessary to dissect the inferior aspect of the cord. Once the dissection is complete, a tension free repair will be performed using a piece of polypropylene mesh. The size of the prosthesis will be at least 3 by 5 inches (7.62 cm x 12.7 cm). Any direct defect will be overlapped by a minimum of 2 cm of mesh. If needed, a second piece of mesh will be used and its size recorded. Whether or not the sac is tucked-up will be recorded. Staples or tacks will be used for fixation and the number and location of staples or tacks will be recorded. The minimal number of tacks will be one tack in the tubercle with the mesh. There will be another tack placed just medial to the vein on Cooper's ligament. A third tack will be placed on the outer edge of the mesh just above the iliopectic track superomedial to the anterior superior spine.

If at any time intra-abdominal viscera are seen, the peritoneal sac will be closed. The method of closure will be recorded. In order to avoid injury to the lateral femoral cutaneous nerve of the thigh or the femoral branch of the genitofemoral nerve, care will be taken not to staple below the iliopectic tract when lateral to the internal spermatic vessels. Staples will be oriented parallel to the nerves, that is, vertically when stapling inferiorly. Superior and lateral placement of staples will be horizontal, corresponding to the direction of the ilioinguinal and iliohypogastric nerves. Additional analgesia (20 cc of dilute marcaine - 10 cc of 0.5% marcaine mixed with 20 cc of saline) may be instilled into the operative space and will be recorded.

Any tissue site 10 mm or greater will be closed. The method of closure, whether it be direct suture or device suturing, will be recorded. Bilateral hernias will be repaired using two pieces of mesh that are overlapped in the middle. The skin will be closed with subcuticular sutures.

## 2. Conventional herniorrhaphy

### LICHTENSTEIN

The local anesthesia technique of Lichtenstein (see below) will be used. The technique described by Lichtenstein et al (video reference) will be used. A 6-cm skin incision is made. The external oblique aponeurosis will be opened including the external ring. If an indirect hernia is found, the sac will either be inverted without division when possible, or divided leaving the distal portion in situ and closing the prenasal sac. This will be recorded. If a direct hernia is identified, the sac will simply be inverted using an absorbable suture purse string. A prosthesis measuring approximately 8 cm x 14 cm will be placed in the defect. The lower edge of the prosthesis will be sutured to Poupart's ligament beginning medially overlapping 2 cm onto the pubic tubercle and proceeding laterally along the ligament beyond the internal ring using 3 to 4 bites of a running 2-0 prolene suture, ending just lateral to the internal ring. If a femoral defect is suspected, the inferior edge of the prosthesis will be sutured to Cooper's ligament, beginning near the area of the pubic tubercle and continuing laterally along Cooper's ligament. A transition stitch would then be accomplished between the prosthesis, Cooper's ligament, the femoral

sheath, and Poupart's ligament and the repair then continued laterally along Poupart's ligament to just lateral to the internal ring. The superior medial border of the prosthesis will be secured to the rectus sheath with an interrupted 2-0 prolene suture creating a wrinkle in the mesh. The superior border of the mesh will be tacked to the internal oblique with an interrupted 2-0 prolene suture. A slit will be made transversely in the mesh from the lateral aspect to the location of the internal ring. The upper and lower portions of the mesh will be brought around the cord. The lower border of the upper portion and the lower border of the lower portion are then tacked to the inguinal ligament just lateral to the internal ring with an interrupted 2-0 prolene suture, recreating the shutter mechanism of the internal ring. The tails of the mesh will be placed laterally under the external oblique. Management of the cremasteric muscles will be recorded. Additional analgesia (20 cc of dilute marcaine - 10 cc of 0.5% marcaine mixed with 20 cc of saline) may be instilled into the operative site and will be recorded. The external oblique fascia is then closed and the skin is closed with a running subcuticular suture.

### 3. Local Anesthesia Technique of Lichtenstein

Use a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine.

1. Subdermic infiltration: 5 ml of mixture infiltrated along line of incision using 2-inch 23-gauge needle. Withdraw needle to intradermal level.
2. Intradermic: Inject intradermally, forming a skin wheel, using approximately 3 ml.
3. Deep subcutaneous injection: 10 ml is injected into deep subcutaneous tissue by vertical insertions of the needle, 2 centimeters apart.
4. Subfascial infiltration: 8-10 ml is injected immediately underneath the aponeurosis of the external oblique through a window created in the subcutaneous adipose tissue at the lateral corner of the incision.
5. Pubic tubercle and hernia sac injection: a few milliliters may be infiltrated at the pubic tubercle, around the neck, and inside the indirect hernia sac.

Reference:  
Kawai, Ph, Shihara, AG, Lichtenstein, R. "Local Anesthesia for Inguinal Hernia Repair Step-by-Step Procedure." *Annals of Surgery* 200(6): 725-735, 1994.

### Coumadin/ASA/NSAID Protocol

ASA/NSAID - Patients taking aspirin or NSAIDs do not need to stop their ASA or NSAIDs prior to surgery. If the patient is on tylenol, it should be stopped and the patient placed on ASA.

Heparin - Pre-op heparin should be stopped 6 hours prior to surgery and restarted 12 hours post-op without a bolus.

Coumadin - [To be approved by individual patient's primary care physician or cardiologist, if

applicable.] Coumadin should be stopped for four days (four doses) prior to surgery and restarted as soon as possible after surgery. "Patients would be expected to have a subtherapeutic INR for approximately two days before surgery, and two days after surgery. However, because the INR will be elevated to some extent for much of this period, patients can still be expected to have partial protection against thromboembolism." (NEJM 336(21): 1506-1511)

	Pre-op Heparin	Post-op Heparin	Comments
Acute DVT Month 1	+	+	Heparin while INR < 2.0
Acute DVT Month 2-3	+	+	
Acute DVT > 3 Months	+	++	*Consider LMW heparin with compression stockings and pneumatic compression devices
Recurrent DVT	+	++	**same as above
Non-valvular A fib	+	+	
Non-valvular A fib with previous embolism	+	+	
Mechanical heart valve	+	+	
Arterial embolism < 1 month	+	+++	***Use heparin only when risk of bleeding is low

References:  
Corson JE, Griffin BD, Roberts DE, McMahon MJ. "Platelet production time in surgery." *Scand J Haematol* 1980; 25(2): 127-133.

Bartley, CV, Wendt RA. "Surgical bleeding associated with aspirin and nonsteroidal anti-inflammatory agents." *Mayo Clinic Proc* 1992; 67(4): 402-3.

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## ENDPOINTS

- The study hypotheses state the effects we expect the interventions to have on the endpoints or outcomes chosen for the study
- In general, choose a single response variable for the primary endpoint

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## PRIORITY OF ENDPOINTS

- Primary Endpoint
  - Response variable chosen to show efficacy
- Secondary Endpoints
  - May be related to the primary endpoint or may be a separate indication of efficacy
  - Must consider multiplicity when making statistical inference
- Tertiary or Additional Endpoints
  - More exploratory in nature

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## TRADEOFFS IN CHOOSING ENDPOINTS

- Maximize the quality and amount of outcome information collected while optimizing work load and minimizing cost
- Too many endpoints lead to loss of focus

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## CHOOSING ENDPOINTS

- Clinically important
- Generally accepted
- Greatest impact
- Response to intervention
- Reliably determined
- Reproducible
- Uniformly collected among sites
- Complete ascertainment

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## BE WARY OF SURROGATE ENDPOINTS

- May be correlated to disease but not involve the same pathophysiologic pathway
- May affect only one pathway of disease
- May affect the true clinical outcome by unintended mechanisms of action that are independent of the disease process

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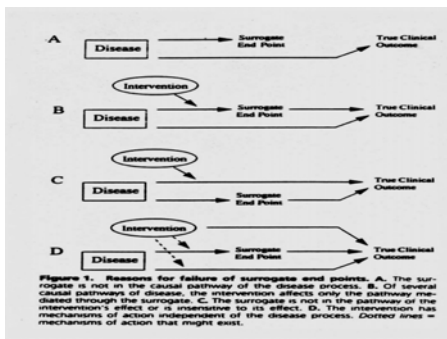
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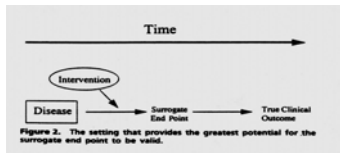
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## Hypertension Studies

- 1960s:VA Cooperative Study of Antihypertensive Treatment for Moderate to Severe Hypertension
  - Established that BP reduction results in reduction in stroke and overall mortality
- 1970s-1990s
  - Many hypertension studies using BP reduction as the primary outcome measure

## Hypertension Studies

- Are all BP drugs equally beneficial?
  - Only diuretics and beta-blockers shown to reduce mortality
  - Concern about side effects for diuretics and beta blockers
  - Possible increase mortality from short acting calcium channel blockers
- Perhaps BP reduction is not a good surrogate endpoint?
- ALLHAT:
  - Will compare mortality rates among groups of patients treated with one of several BP drugs

## Be Wary of Composite Endpoints

- Why a composite endpoint?
  - Usually to obtain enough events to keep the sample size manageable
- Combining Apples and Oranges?
  - Combining efficacy measures with drug side effects
  - Combining several types of events with very different levels of severity
    - Death
    - Stroke
    - TIA

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## VALIDATION OF STUDY ENDPOINTS

- Develop a strict protocol definition
- Unbiased
- Identify required source documentation

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## VALIDATION OF STUDY ENDPOINTS

- Will any of the following be required and affordable?
  - Laboratory confirmation
  - Central readings
  - Central review of evidence
  - Adjudication by Endpoints Committee

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**“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”**

JW Tukey, 1962

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